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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
NGUYEN, QUANG	

ART UNIT	PAPER NUMBER
1633	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/575,232	WITTE ET AL.	
	Examiner	Art Unit	
	QUANG NGUYEN, Ph.D.	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *23 June 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-16* is/are pending in the application.

4a) Of the above claim(s) *13, 15-16* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-12 and 14* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *07 April 2006* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *1/26/07;8/27/07*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

This application was transferred to examiner Quang Nguyen, Ph.D. in AU 1633.

Claims 1-16 are pending in the present application.

Applicant's election with traverse of Group I as to Group II but without traverse as to Group III in the reply filed on 6/23/08 is acknowledged. The traversal is on the ground(s) that although the method of Group II is a combination that includes the method of Group I, the cited prior art is not detrimental to the common inventive concept; and therefore the claims of Group II should be considered with the claims of Group I This is not found persuasive because as already noted in the Office action mailed on 5/23/2003 (page 3, first two paragraphs), the subcombination of Group I is not a contribution over the cited prior art and therefore there is no inventive link between the methods of Groups I and II.

The requirement is still deemed proper and is therefore made FINAL.

The examiner notes that claim 14 should be grouped together with claims of Group I because it is directly dependent on claim 1 and it is more limited in scope.

Claims 13 and 15-16 are withdrawn from further consideration because they are directed to non-elected inventions.

Accordingly, claims 1-12 and 14 are examined on the merits herein.

Claim Objections

Claims 1 and 3 are objected to because of the term "extra cellular". The term should be one word "extracellular". Appropriate correction is required.

Claim 11 is objected to because of an inadvertent misspelling of the term "inMol" on line 5 of the claim. Appropriate correction is required.

Claim 8 is objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. This is because in claim 6 from which claim 8 is dependent, chondrocytes are already isolated from a mammal.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 10-12 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 11 recites the limitation "said mammal" in line 4 of the claim. There is insufficient antecedent basis for this limitation in the claim. This is because in claim 1 from which claim 11 is dependent, there is no recitation of any mammal.

A broad range or limitation together with a narrow range or limitation that falls within the broad range or limitation (in the same claim) is considered indefinite, since the resulting claim does not clearly set forth the metes and bounds of the patent protection desired. See MPEP § 2173.05(c). Note the explanation given by the Board of Patent Appeals and Interferences in *Ex parte Wu*, 10 USPQ2d 2031, 2033 (Bd. Pat.

App. & Inter. 1989), as to where broad language is followed by "such as" and then narrow language. The Board stated that this can render a claim indefinite by raising a question or doubt as to whether the feature introduced by such language is (a) merely exemplary of the remainder of the claim, and therefore not required, or (b) a required feature of the claims. Note also, for example, the decisions of *Ex parte Steigewald*, 131 USPQ 74 (Bd. App. 1961); *Ex parte Hall*, 83 USPQ 38 (Bd. App. 1948); and *Ex parte Hasche*, 86 USPQ 481 (Bd. App. 1949). In the present instance, claim 10 recites the broad recitation "the cells" and the claim also recites "preferably chondrocytes", which is the narrower statement of the range/limitation.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-2, 4-8 and 14 are rejected under 35 U.S.C. 102(b) as being anticipated by Egerbacher et al. (Vet Pathol 38:143-148, 2001; Cited previously).

Egerbacher et al already teach that magnesium supplementation at 1X concentration (0.0612 mg/ml MgCl + 0.0488 mg/ml MgSO4 = 1mM MgCl + 0.4 mM MgSO4) or at 3X concentration (about 4.2 mM Mg) has a significantly positive effect on quinoline-treated horse and dog chondrocytes in 5-day cultures containing 10% FCS; and that chondrotoxic quinolones are important antibacterial drugs in human and

veterinary medicine (see at least the abstract; Figures 1-5; page 144, col. 1, second paragraph; and section titled "Magnesium supplementation"). Positive effects of Mg supplementation include decreased cell loss and morphologic changes (outspread, stellate chondrocytes vs more spindle-shaped or spherical cells of quinolone-treated and Mg-free chondrocytes). Egerbacher et al further disclose that the addition of Mg2+ slightly increased cell proliferation (53% for Mg1 and 55% for Mg3) with respect to cells cultivated in Mg2+-free medium (47%; see page 146, col. 1, second paragraph; Figure 6). The term "unphysiologically high extracellular concentration of Mg" is defined in the present application to mean that the concentration of Mg ion in the culture is above the physiological level normally present in the body the cells are derived from, for example in humans any concentration of Mg in the extracellular compartment above 0.9 mM (page 7, lines 12-19). Additionally, it should be noted that FCS contains a growth factor; and that isolated chondrocytes of Egerbacher et al are indistinguishable from chondrocytes differentiated from chondrocyte precursor cells or mesenchymal stem cells.

Accordingly, the teachings of Egerbacher et al meet every limitation of the instant claims as written. Therefore, the reference anticipates the instant claims.

Claims 1 and 3-4 are rejected under 35 U.S.C. 102(b) as being anticipated by Valletta, G. (US 6,248,368; IDS).

Since the term "cultivation of cells" is intended to mean that the cells are kept under conditions allowing the cells to growth and/or to differentiate in either in vivo or in

vitro as defined by the present application (page 6, line 37 continues to line 2 of page 7); and the term "unphysiologically high extracellular concentration of Mg" is defined to mean that the concentration of Mg ion in the culture is above the physiological level normally present in the body the cells are derived from, for example in humans any concentration of Mg in the extracellular compartment above 0.9 mM (page 7, lines 12-19); the following rejection is applied. Please also note that the term "cells" in the rejected claims is not necessarily limited to chondrocytes but to any cells.

Valletta already discloses a method for treating autoimmune diseases, including rheumatoid arthritis, systemic lupus erythematosus and others, by administering orally or parenterally a pharmaceutically acceptable composition suitable for releasing magnesium ions (e.g., organic or inorganic magnesium salts or complexes thereof) to a patient in need thereof (see at least the abstract; col. 3, line 31 continues to line 11 of col. 6). Valletta further discloses that magnesium can be an organic salt, such as magnesium lactate, aspartate or acetate or an inorganic salt, such as magnesium pyrophosphate, pidolate (col. 4, lines 54-65).; and that the therapeutic dose for oral administration ranges from 2 to 12 mg of magnesium per kg of body weight or from 2 to 30 mg/kg body weight daily for parenteral administration such as intramuscular and intravenous injections (col. 5, lines 12-57). Valletta further teaches in the frame of the magnesium therapy, the blood magnesium level should be monitored to prevent any magnesium excess of over 1.5 nmol/l or 1.5 mM; and any magnesium excess can be treated with intravenous administration of calcium, osmotic diuresis and others (col. 5, line 57 continues to line 11 of col. 6). In exemplifications, Valletta teaches a daily

infusion of about 489 mg Mg in 500 cm^3 of physiologic solution (equivalent about 40 mM Mg concentration) into a 35-year-old woman showed symptoms of an acute migrant arthritis at the wrists, at the scapula-humerus and at the dorsum pedis articulation (col. 8, line 45 continues to line 9 of col. 9); as well as a daily infusion via intravenous route of about 733 mg Mg in 500 cm^3 of a physiologic solution (equivalent about 60 mM Mg concentration) into a 32-year-old patient affected by a pemphigus vulgaris (col. 9, lines 28-52). Please note that in the later exemplification, the unphysiologically high Mg concentration is in contacted with blood cells in the presence of the same patient's serum. Accordingly, the method taught by Valletta et al has the same broad method step as the broadly claimed method; and therefore the teachings of Valletta meet every limitation of the instant claims as written.

Thus, the reference anticipates the instant claims.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation

under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-12 and 14 are rejected under 35 U.S.C. 103(a) as being unpatentable over Masuda et al. (US 2001/0012965) in view of Egerbacher et al. (Vet Pathol 38:143-148, 2001; Cited previously), Valletta, G. (US 6,248,368; IDS) and Halvorsen et al. (US 6,841,150).

Masuda et al already disclose at least a method for producing a transplantatble cartilage matrix, comprising culturing isolated chondrogenic cells, including human adult articular chondrocytes, in alginate culture containing a stimulatory agent, such as fetal bovine serum and/or exogenously added specific growth factors such as osteogenic protein-1, TGF-beta, insulin like growth factor, for an amount of time effective for allowing formation of a chondrogenic cell-associated matrix (see at least Summary of the Invention; and particularly paragraphs 33-40 and example 1).

Masuda et al did not teach a method of culturing isolated chondrogenic cells in the presence of an unphysiologically high extracellular concentration of magnesium, including the concentration of magnesium in the range of about 12 mM to about 65 mM or in the range of 11 to 25 mM or in the range of 21 to 65 mM; and under an oxygen partial pressure of 8%.

However, at the effective filing date of the present application Egerbacher et al already taught that magnesium supplementation at 1X concentration (0.0612 mg/ml

MgCl + 0.0488 mg/ml MgSO4 = 1mM MgCl + 0.4 mM MgSO4) or at 3X concentration (about 4.2 mM Mg) has a significantly positive or protective effect on quinoline-treated horse and dog chondrocytes in 5-day cultures, with more positive effects observed for a triple dose (see at least the abstract; Figures 1-5; page 144, col. 1, second paragraph; and section titled "Magnesium supplementation"). Egerbacher et al further disclosed that the addition of Mg2+ slightly increased cell proliferation (53% for Mg1 and 55% for Mg3) with respect to cells cultivated in Mg2+-free medium (47%; see page 146, col. 1, second paragraph; Figure 6).

Additionally, Valletta already discloses a method for treating autoimmune diseases, including rheumatoid arthritis, systemic lupus erythematosus and others, by administering orally or parenterally a pharmaceutically acceptable composition suitable for releasing magnesium ions (e.g., organic or inorganic magnesium salts or complexes thereof) to a patient in need thereof (see at least the abstract; col. 3, line 31 continues to line 11 of col. 6). In exemplifications, Valletta taught a daily infusion of about 489 mg Mg in 500 cm^3 of physiologic solution (equivalent about 40 mM Mg concentration) into a 35-year-old woman showed symptoms of an acute migrant arthritis at the wrists, at the scapula-humerus and at the dorsum pedis articulation (col. 8, line 45 continues to line 9 of col. 9); as well as a daily infusion via intravenous route of about 733 mg Mg in 500 cm^3 of a physiologic solution (equivalent about 60 mM Mg concentration) into a 32-year-old patient affected by a pemphigus vulgaris (col. 9, lines 28-52).

Moreover, at the effective filing date of the present application Halvorsen also disclosed at least a method for directing adipose-derived stromal cells cultivated *in vitro*,

including in a calcium alginate or another biocompatible lattice or matrix capable of supporting chondrogenesis in a three dimensional configuration, to differentiate into chondrocyte lineage in conditions such as at temperatures between 31 °C to 37 °C in a humidified incubator, with a carbon dioxide content to be maintained between 2% to 10% and the oxygen content between 1% and 22% (see at least Summary of Invention; particularly col. 5, line 54 continues to line 7 of col. 6; col. 6, lines 61-65).

It would have been obvious for an ordinary skilled artisan to modify the teachings of Masuda et al by also culturing isolated chondrogenic cells in the presence of a high extracellular concentration of Mg, including at any Mg concentration within 11 to 65 mM, as well as culturing the chondrogenic cells under an oxygen partial pressure of 8%, in light of the teachings of Egerbacher et al, Valletta G and Halvorsen et al as discussed above.

An ordinary skilled artisan would have been motivated to carry out the above modifications because Egerbacher et al already showed at least protective effects of Mg at a 4.2 mM (triple dose) for horse and dog chondrocytes against quinolones in tissue cultures, and that Mg2+ supplementation slightly increased cell proliferation. Additionally, Valletta also showed by exemplifications the use of Mg concentrations of 40 mM and 60 mM for infusion into a patient. Furthermore, cultivation of adipose-derived stromal cells in a calcium alginate culture to differentiate into chondrocyte lineage in an oxygen content between 1% and 22% was also taught by Halvorsen et al.

An ordinary skilled artisan would have a reasonable expectation of success in light of the teachings of Masuda et al, Egerbacher et al, Valletta, G, and Halvorsen et al; coupled with a high level of skill for an ordinary skilled artisan in the relevant art.

Therefore, the claimed invention as a whole was *prima facie* obvious in the absence of evidence to the contrary.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Quang Nguyen, Ph.D., whose telephone number is (571) 272-0776.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's SPE, Joseph T. Woitach, Ph.D., may be reached at (571) 272-0739.

To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Group Art Unit 1633; Central Fax No. (571) 273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

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/QUANG NGUYEN, Ph.D./
Primary Examiner, Art Unit 1633